IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Xianzhong Yu et al.	Title:	Lytic Peptide Prodrugs
App. No.:	09/938,623	Art Unit:	1643
Conf. No.:		Examiner:	Karen A. Canella
Filing Date:	August 27, 2001		

RESPONSE TO NON-FINAL OFFICE ACTION

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This paper is filed in response to the non-final office action mailed on August 20, 2007 for the above-identified patent application and is accompanied by a request for a three month extension of time. The Commissioner is authorized to deduct the requisite fee for the extension of time from Howrey LLP deposit account No. 08-3038, referencing the above-identified attorney docket number. No other fee is believed to be due at this time, but he Commissioner is authorized to deduct any additional fees that may be deemed necessary for further prosecution of the above-identified patent application from Howrey LLP deposit account No. 08-3038, referencing the above-identified attorney docket number.

I. AMENDMENTS TO THE CLAIMS

Please amend the pending claims as follows:

1. (Cancelled).

2. (Cancelled).

3. (Cancelled).

4. (Cancelled).

5. (Cancelled).

6. (Cancelled).

7. (Currently Amended) ~~**The procytotoxin of claim 6, further**~~ **A procytotoxin** comprising at least one lysine residue bound via a peptide bond to at least one amino acid via the ε-amino group of said lysine residue **and further comprising a cytotoxic peptide bound to an inactivator via a peptide bond, wherein said peptide is a pore-forming cytolytic peptide that comprises an amphipathic alpha-helical structure, and wherein said peptide bond is susceptible to cleavage by PSMA.**

8. (Currently Amended) The procytotoxin of claim ~~1~~ 7, further comprising a targeting molecule.

9. (Original) The procytotoxin of claim 8, wherein said targeting molecule is selected from the group consisting of a molecule that targets the neo-vasculature and an antibody.

10. (Original) The procytotoxin of claim 9, wherein said targeting molecule is an RGD targeting sequence.

11. (Cancelled).

12. (Cancelled).

13. (Currently Amended) The procytotoxin of claim ~~1~~ 7, wherein said cytolytic peptide is selected from the group consisting of Ae I, cytolysin of sea anemone, aerolysin, amatoxin, amoebapore, amoebapore homolog from *Entamoeba dispar*, brevinin-1E, brevinin-2E, barbatolysin, cytolysin of *Enterococcus faecalis*, delta hemolysin, diphtheria toxin, E1 Tor cytolysin of *Vibrio cholerae*, equinatoxin, enterotoxin of *Aeromonas hydrophila*, esculentin, granulysin, haemolysin of *Vibrio parahaemolyticus*, intermedilysin of *Streptococcus intermedius*, the lentivirus lytic peptide, leukotoxin of *Actinobacillus actinomycetemcomitans*, magainin, melittin, membrane-associated lymphotoxin, Met-enkephalin, neokyotorphin, neokyotorphin fragment 1, neokyotorphin fragment 2, neokyotorphin fragment 3, neokyotorphin fragment 4, NK-lysin, paradaxin, perforin, perfringolysin O, theta-toxin, of *Clostridium perfringens*, phallolysin, phallotoxin, streptolysin, D,L-α-amino acid cyclic peptides.

14. (Currently Amended) The procytotoxin of claim ~~1~~ 7, wherein said cytolytic peptide is a melittin.

15. (Previously Presented) The procytotoxin of claim 14, wherein said cytolytic peptide comprises the following structure: Gly-Ile-Gly-Ala-Val-Leu-Lys-Val-Leu-Thr-Thr-Gly-Leu-Pro-Ala-Leu-Ile-Ser-Trp-Ile-Lys-Arg-Lys-Arg-Gln-[Gln-Gly-Ala-Ile-Gly-Gln-Pro] (residues 1-32 of SEQ ID NOS 1 or 2).

16. (Original) The procytotoxin of claim 15, further comprising a targeting molecule.

17. (Original) A pharmaceutical composition, comprising one or more procytotoxins of claim 15 and a pharmaceutically suitable carrier or excipient.

18. (Previously Presented) The procytotoxin of claim 14, wherein said cytolytic peptide comprises the following structure: Gly-Ile-Gly-Ala-Val-Leu-Lys-Val-Leu-Thr-Thr-Gly-Leu-Pro-Ala-Leu-Ile-Ser-Trp-Ile-Lys-Arg-Lys-Arg-Gln-[Gln- Ser-Ser-Phe(or Tyr)-Tyr-Ser-Gly(or Ser)] (residues 1-32 of SEQ ID NOS 3 or 4).

19. (Original) The procytotoxin of claim 18, further comprising a targeting molecule.

20. (Original) A pharmaceutical composition, comprising one or more procytotoxins of claim 18 and a pharmaceutically suitable carrier or excipient.

21. (Currently Amended) A pharmaceutical composition, comprising one or more procytotoxins of claim ~~1~~ 7 and a pharmaceutically suitable carrier or excipient.

22. (Cancelled).

23. (Cancelled).

24. (Cancelled).

25. (Cancelled).

26. (Cancelled).

27. (Cancelled).

28. (Currently Amended) ~~**The method of claim 27**~~, **A method for selectively destroying a target cell, comprising contacting the target cell with a procytotoxin, which comprises a cytotoxic peptide bound via a peptide bond to an inactivator, wherein said peptide is a pore-forming cytolytic peptide that comprises an amphipathic alpha-helical structure,** wherein said procytotoxin further comprises at least one lysine residue bound via a peptide bond to at least one amino acid via the ε-amino group of said lysine residue, **and wherein said peptide bond is susceptible to cleavage by PSMA.**

29. (Currently Amended) The method of claim ~~22~~ 28, wherein said procytotoxin further comprises a targeting molecule.

30. (Original) The method of claim 29, wherein said targeting molecule is selected from the group consisting of a molecule that targets the neo-vasculature and an antibody.

31. (Original) The method of claim 30, wherein said targeting molecule is an RGD targeting sequence.

32. (Cancelled).

33. (Cancelled).

34. (Currently Amended) The method of claim ~~22~~ **28**, wherein said cytolytic peptide is selected from the group consisting of Ae I, cytolysin of sea anemone, aerolysin, amatoxin, amoebapore, amoebapore homolog from *Entamoeba dispar*, brevinin-1E, brevinin-2E, barbatolysin, cytolysin of *Enterococcus faecalis*, delta hemolysin, diphtheria toxin, E1 Tor cytolysin of *Vibrio cholerae*, equinatoxin, enterotoxin of *Aeromonas hydrophila*, esculentin, granulysin, haemolysin of *Vibrio parahaemolyticus*, intermedilysin of *Streptococcus intermedius*, the lentivirus lytic peptide, leukotoxin of *Actinobacillus actinomycetemcomitans*, magainin, melittin, membrane-associated lymphotoxin, Met-enkephalin, neokyotorphin, neokyotorphin fragment 1, neokyotorphin fragment 2, neokyotorphin fragment 3, neokyotorphin fragment 4, NK-lysin, paradaxin, perforin, perfringolysin O, theta-toxin, of *Clostridium perfringens*, phallolysin, phallotoxin, streptolysin, D,L- α-amino acid cyclic peptides.

35. (Currently Amended) The method of claim ~~22~~ **28**, wherein said cytolytic peptide is a melittin.

36. (Previously Presented) The method of claim 35, wherein said cytolytic peptide comprises the following structure: Gly-Ile-Gly-Ala-Val-Leu-Lys-Val-Leu-Thr-Thr-Gly-Leu-Pro-Ala-Leu-Ile-Ser-Trp-Ile-Lys-Arg-Lys-Arg-Gln-[Gln-Gly-Ala-Ile-Gly-Gln-Pro] (residues 1-32 of SEQ ID Nos 1 or 2).

37. (Original) The method of claim 36, further comprising a targeting molecule.

38. (Previously Presented) The method of claim 35, wherein said cytolytic peptide comprises the following structure: Gly-Ile-Gly-Ala-Val-Leu-Lys-Val-Leu-Thr-Thr-Gly-Leu-Pro-Ala-Leu-Ile-Ser-Trp-Ile-Lys-Arg-Lys-Arg-Gln-[Gln-Ser-Ser-Phe(or Tyr)-Tyr-Ser-Gly(or Ser)] (residues 1-32 of SEQ ID Nos 3 or 4).

39. (Original) The method of claim 38, further comprising a targeting molecule.

40. (Cancelled).

41. (Cancelled).

42. (Cancelled).

43. (Cancelled).

44. (Cancelled).

45. (Cancelled).

46. (Currently Amended) ~~**The method of claim 45,**~~ **A method of making a procytotoxin, comprising modifying a cytotoxic peptide to include an inactivator, wherein said cytoxic peptide is a pore-forming cytolytic peptide that comprises an amphipathic alpha-helical structure;** wherein said procytotoxin further comprises at least one lysine residue bound via a peptide bond to at least one amino acid via the ε-amino group of said lysine residue**, and wherein said targeting specific protease is a PSMA**.

47. (Currently Amended) The method of claim ~~**40**~~ **46**, wherein said procytotoxin further comprises a targeting molecule.

48. (Original) The method of claim 47, wherein said targeting molecule is selected from the group consisting of a molecule that targets the neo-vasculature and an antibody.

49. (Original) The method of claim 48, wherein said targeting molecule is an RGD targeting sequence.

50. (Cancelled).

51. (Cancelled).

52. (Currently Amended) The method of claim ~~**40**~~ **46,** wherein said cytolytic peptide is selected from the group consisting of Ae I, cytolysin of sea anemone, aerolysin, amatoxin, amoebapore, amoebapore homolog from *Entamoeba dispar*, brevinin-1E, brevinin-2E, barbatolysin, cytolysin of *Enterococcus faecalis*, delta hemolysin, diphtheria toxin, E1 Tor cytolysin of *Vibrio cholerae*, equinatoxin, enterotoxin of *Aeromonas hydrophila*, esculentin, granulysin, haemolysin of *Vibrio parahaemolyticus*, intermedilysin of *Streptococcus intermedius*, the lentivirus lytic peptide, leukotoxin of *Actinobacillus actinomycetemcomitans*, magainin, melittin, membrane-associated lymphotoxin, Met-enkephalin, neokyotorphin, neokyotorphin fragment 1, neokyotorphin fragment 2, neokyotorphin fragment 3, neokyotorphin

fragment 4, NK-lysin, paradaxin, perforin, perfringolysin O, theta-toxin, of *Clostridium perfringens*, phallolysin, phallotoxin, streptolysin, D,L-α-amino acid cyclic peptides.

53. (Currently Amended) The method of claim ~~40~~ **46**, wherein said cytolytic peptide is a melittin.

54. (Currently Amended) The method of claim **46, ~~making a procytotoxin, comprising modifying a cytotoxic peptide to include an inactivator, wherein said cytotoxic peptide is a pore-forming cytolytic peptide, and~~** wherein said pore-forming cytolytic peptide comprises the following structure: Gly-Ile-Gly-Ala-Val-Leu-Lys-Val-Leu-Thr-Thr-Gly-Leu-Pro-Ala-Leu-Ile-Ser-Trp-Ile-Lys-Arg-Lys-Arg-Gln-[Gln-Gly-Ala-Ile-Gly-Gln-Pro] (residues 1-32 of SEQ ID NOS 1 or 2).

55. (Original) The method of claim 54, further comprising adding a targeting molecule to said procytotoxin.

56. (Original) The method of claim 55, further comprising adding a targeting molecule to said procytotoxin.

57. (Previously Presented) The method of claim 53, wherein said cytolytic peptide comprises the following structure: Gly-Ile-Gly-Ala-Val-Leu-Lys-Val-Leu-Thr-Thr-Gly-Leu-Pro-Ala-Leu-Ile-Ser-Trp-Ile-Lys-Arg-Lys-Arg-Gln-[Gln-Ser-Ser-Phe(or Tyr)-Tyr-Ser-Gly (or Ser)] (residues 1-32 of SEQ ID NOS 3 or 4).

58. (Currently Amended) The method of claim ~~40~~ **28**, wherein said target cell is a cancer cell.

59. (Original) The method of claim 58 wherein said cancer cell is selected from the group consisting of prostate, ovarian, breast, skin, lung and pancreas.

60. (Original) A method of treating a cancer patient, comprising administering a therapeutically effective amount of the pharmaceutical composition of claim 21.

61. (New). The procytotoxin of claim 7, wherein said inactivator is selected from the group consisting of a microbead, an amino acid, a peptide, phage and a phage filament.

62. (New). The method of claim 28, wherein said inactivator is selected from the group consisting of a microbead, an amino acid, a peptide, phage and a phage filament.

63. (New). The method of claim 46, wherein said inactivator is selected from the group consisting of a microbead, an amino acid, a peptide, phage and a phage filament.

II. ARGUMENTS AND REMARKS

A. Claim Rejections Under 35 U.S.C. §112, Second Paragraph, Should be Withdrawn

At page 2 of the Office Action, the Examiner rejected pending claims 58 and 59 allegedly as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner further explained that the recitation of "said target cell" lacks proper antecedent basis in claim 40 from which claim 58 depends.

With this response, Applicants amend claim 58. As amended, claim 58 and its dependent claim 59 depend from claim 28 which provides proper antecedent basis for "said target cell." The amendment does not introduce new matter and is fully supported by the specification as filed. *See*, e.g., paragraphs [0096] and [0097]. Therefore, the Examiner may properly withdraw the rejection of claims 58 and 59 under U.S.C. §112, second paragraph, and withdrawal is respectfully requested.

B. Claim Objections

The Examiner objected to claims 7, 15-20, 28, 36-39, 46 and 54-57 because of their dependency from the rejected claims. However, the Examiner indicated that the claims would be allowable if rewritten in an independent form.

With this response, Applicants amend claims 7, 28 and 46 by rewriting them in an independent form. As currently amended, claims 7, 28 and 46 do not introduce new matter and are fully supported by the specification as filed. Applicants respectfully submit that because claims 7, 28 and 46 are rewritten in an independent form, Applicants have overcome the Examiner's objection to the claims and their dependent claims 15-20, 36-39, and 54-57. Therefore, Applicants respectfully believe that claims 7, 15-20, 28, 36-39, 46 and 54-57, as currently amended, are allowable.

C. Claim Rejections Under 35 USC §102(b) and 35 USC §103(a) Are Moot

At page 2 of the Office Action, the Examiner rejected pending claims 1-3, 5, 8, 13, 14, 21-24, 26, 29, 34, 35, 40-42, 44, 47, 52, 53, 58-60 under 102(b) as being anticipated by WO 97/33908 to Rivett (*Rivett*).

At page 4 of the Office Action, the Examiner rejected claims 1-6, 8-10, 13, 14, 21-27, 29-31, 34, 35, 40-45, 47-49 and 52, 53, 58-60 under 35 USC §103(a) as being unpatentable over *Rivett* in view of *Glazier* (U.S. 2003/0138432), *Thorpe* (U.S. 6,342,219) *and Rawlings* (Biochimica et Biophysica Acta, 1997).

At page 6 of the Office Action, the Examiner rejected claims 1-3, 5, 8, 9, 11, 13, 14, 21-24, 26, 29, 30, 32, 34, 35, 40, 42, 44, 47, 48, 50, 52, 53, 58-60 under 35 USC §103(a) as being unpatentable over *Rivett* in view of *Neri.*

With this response and without acquiescing to the rejections and exclusively for the purpose of expediting prosecution of the above-identified patent application, Applicants now cancel without prejudice claims 1-6, 22-27, 40-45 and reserve the right to present the cancelled claims in a duly filed continuation application.

With this response, Applicants also amend rejected dependent claims 8, 13, 14, 21, 29, 34, 35, 47, 52, 53, 54. As currently amended, the claims no longer depend from the cancelled claims and instead depend from claims 7, 28 and 46 now rewritten in an independent form.

Applicants respectfully submit that in view of the fact that claims 1-6, 22-27, 40-45 are cancelled without prejudice with this response and their dependent claims 8, 13, 14, 21, 29, 34, 35, 47, 52, 53, 54 are amended as discussed above, the rejections under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) may be properly withdrawn as moot; and withdrawal is respectfully requested.

D. New Dependent Claims 61, 62 and 63

With this response, Applicants also add new dependent claims 61, 62 and 63. The claims do not introduce new matter and are fully supported by the specification as filed.

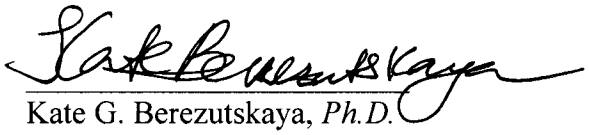
III. CONCLUSION

In view of the above amendments and arguments, Applicants respectfully submit that the instant application is in good and proper order for allowance and early notification to this effect is respectfully solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at (312) 846 5622.

Respectfully submitted,

HOWREY LLP

Dated: February 20, 2008

By: 

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